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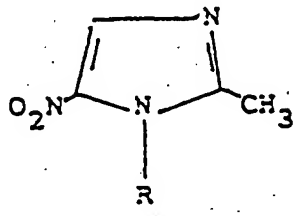
(54) Title: NOVEL USE OF NITROIMIDAZOLES



(I)

(57) Abstract

The use of a compound of formula (I) wherein R is: a) $-(CH_2)_mSO_2(CH_2)_nCH_3$ where m = 2-3 and n = 0-1; or b) $-(CH_2)_mSO_2CH(CH_3)_2$ where m = 2-3 for the preparation of a pharmaceutical composition for the treatment, especially the topical treatment, of inflammatory and/or infectious skin conditions.

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Novel use of nitroimidazoles.

Technical Field

The present invention relates to a novel pharmaceutical use of a specific group of imidazoles known per se in the past and also known in a medical context. More particularly, the invention relates to the use of the above compounds for the preparation of a pharmaceutical composition for the treatment of inflammatory and/or infectious skin conditions.

Background of the invention

Acne vulgaris is a disease state which is distinguished by infected and blocked up sebaceous glands with inflammation in the surrounding tissue.

Acne often commences with hyperproliferation of corneocytes and the formation of an adhesive generating structure which binds the corneocytes together and forms a plug in the sebaceous gland canal. These closed comedones, also known as "whiteheads", are the first stage of acne. The closed comedones develop further into open comedones, "blackheads", or to inflammatory lesions of the papula or pustule type. These can then deepen and form cystic acne. Common to all of these conditions is the presence of large numbers of Proprionibacterium acnes, P. acnes.

The treatment of acne is diversified. Superficial and moderately severe acne, acne vulgaris, is locally treated especially with benzoyl peroxide, antibiotics and vitamin A derivatives. Benzoyl peroxide gives a complete recovery in around 60% of cases, but often causes side effects in the form of redness, irritation and dryness. An increase

in the frequency of a cancer, melanoma, after treatment with benzoyl peroxide is currently under discussion in the literature (see Jones G.R.N, Human Toxicology, (1985) 77: pp 413-421, "Skin Cancer: Risk to Individuals"). Antibiotics provide recovery frequencies of the same order of magnitude as for benzoyl peroxide. Lately, falling efficacy linked to the development of resistance has been mooted. Vitamin A derivatives have good efficacy against acne except for local side effects and even teratogenic effects.

Rosacea, previously known as acne rosacea, is a disease state which is distinguished by superficial inflamation, especially in the face. Nowadays, rosacea is treated inter alia with metronidazole.

Seborrhoea is a disease state which is distinguished by desquamating skin, often in conjunction with itching. In severe cases, a crust is formed which gives rise to mixed infections. Seborrhoeic eczema can be regarded partly as an inflammatory reaction and partly as an infection of Pitosporum ovale. Treatment nowadays is with steroids and in simpler cases with selenium sulphide and metronidazole.

In summary, it is apparent that the currently used remedies all exhibit one or more drawbacks as regards the abovementioned disease states.

As foreshadowed above, the compounds which are used according to the present invention are known per from the past. In this connection, the following can be named as examples of references describing the compounds and their preparation:

M.W. Miller, H.L. Howes and A.R. English, Antimicrobial Agents and Chemotherapy, 1969, pp 257-260, "Tinidazole, a potent new antiprotozoal agent";

H. Beckman, Drug Therapy 1963-64, pp 383-384, "Vaginal

trichomoniasis and monoiliasis";

G. Berkelhammer and G. Asato, (1968) Science 162: 1146 "2-amino-5-(1-methyl-5-nitro-2-imidazoyl)-1,2,4-thiadizole: A new microbial agent";

H.L. Howes et al., Antimicrobial Agents and Chemotherapy, 1969, pp 261-266, "Tinidazole, a new antiprotozoal agent"; and

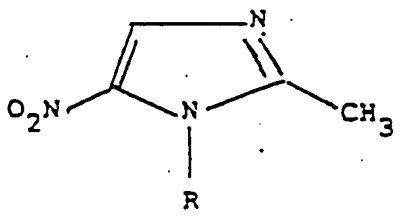
J. Azawa et al., (1965) J.Med.Chem. 8: pp150-153, "Substituent constants for aliphatic..."

Additionally, as regards the efficacy of tinidazole against parasites, for example, a description appears in "Tinidazole: A rew...", (1976) Drugs 11: pp423-440.

Description of the invention

The present invention relates to a novel medical use of known pharmaceutically active substances and more particularly to the use of these for the preparation of a pharmaceutical composition for the treatment or prophylaxis of inflammatory and/or infectious skin conditions or diseases of the type mentioned above. Aside from providing a useful alternative to the abovementioned forms of treatement, the compounds used in accordance with the present invention also enable the elimination or at least reduction of the drawbacks or side effects arising in relation to the known remedies. They are, moreover, of particular interest against a combination of infection and inflammation.

In more concrete terms, the use of the invention relates to the use of a compound of the formula (I)



(I)

wherein R is:

a) $-(CH_2)_mSO_2(CH_2)_nCH_3$
where m = 2-3 and n = 0-1; or

b) $-(CH_2)_mSO_2CH(CH_3)_2$
where m = 2-3

for the preparation of a pharmaceutical composition for the treatment, especially the topical treatment, of inflammatory and/or infectious skin conditions.

Compounds used in accordance with the invention within variant a) are:

methyl(2-(2-methyl-5-nitro-1-imidazolyl)ethyl)sulfone (m = 2, n = 0);
ethyl(2-(2-methyl-5-nitro-1-imidazolyl)ethyl)sulfone (m = 2, n = 1);
methyl(2-(2-methyl-5-nitro-1-imidazolyl)propyl)sulfone (m = 3, n = 0); and
ethyl(2-(2-methyl-5-nitro-1-imidazolyl)propyl)sulfone (m = 3, n = 1).

Compounds within variant b) used in accordance with the invention are:

isopropyl(2-(2-methyl-5-nitro-1-imidazolyl)ethyl)sulfone (m = 2); and
isopropyl(2-(2-methyl-5-nitro-1-imidazolyl)propyl)sulfone (m = 3).

Of the above compounds, the use of ethyl(2-(2-methyl-5-nitro-1-imidazolyl)ethyl)sulfone is particularly preferred.

As indicated above, the compounds used in the practice of the invention are known per se from the past and therefore can be obtained direct from commercial sources or prepared by techniques that are in themselves known, e.g. by analogy to the preparative methods recited in the above mentioned references.

The amount or concentration of the compound used is, of course, selected on the basis of the infectious or inflammatory condition which is to be treated. However, a preferred concentration of the compounds in question is 0.25 to 5 weight percent, calculated on the total weight of the composition, a particularly favoured concentration regime being 0.5 to 2 weight percent, calculated on the same basis.

In other respects the pharmaceutical composition can be prepared by techniques that are in themselves known using known additives, depending on the desired mode of application. Topical application is considered of primary importance in this connection with the preferred modes of application being creams, gels and emulsions. Preparative methods for these dosage forms are, of course, described in innumerable references and need not be further recited here.

A particularly preferred dosage form, however, is one employing "hydrophilic solid crystals". Production of these is described, inter alia, in British patent publication 1,174,672 to which reference is made in this connection.

Generally speaking, however, the latter process requires blending a polar lipid which has the capacity to form said hydrophilic crystals with water or any other polar liquid with corrresponding properties such as glycerol, ethylene glycol or propylene glycol to form a mixture with a

concentration of water or other polar liquid of 50 to 59 weight percent. This mixture is brought to a temperature over the "transition temperature" for the particular lipid, this temperature being defined as the lowest temperature at which a lipid particle in contact with excess water or said polar liquid can absorb water or said polar liquid and be converted to cylindrical or spherical particles, "liposomes", exhibiting strong birefringency. The mixture is maintained over said temperature, with agitation, until conversion has taken place and then cooled under continued agitation to room or some other desired temperature, such that surface active solid crystals are formed. The compound of formula (I) used in accordance with the invention can be added before the lipid in question has been converted to liposomes or while it is still in liposome form.

Examples of conventional additives which can be incorporated in the pharmaceutical composition used in accordance with the invention are conventional carriers, consistency agents or regulators, pH regulators etc.

Particularly preferred embodiments of the invention involve the use of a compound of formula (I) for the treatment of inflammatory and/or infectious skin conditions of the eczema, acne and/or rosacea type. One type of eczema which has been treated effectively in this way is the seborrhoeic variety. In particular, it is thus apparent that the use of the invention can be employed against conditions having their origin in an infectious and an inflammatory component.

Examples

The invention will now be further illustrated with reference to the following non-limiting examples where various dose forms are exemplified.

Example 1

A cream preparation containing the following components was prepared:

1-glycerol monolaurate	7 wt%
1-glycerol monomyristate	21 wt%
Propylene glycol	30 wt%
Tinidazole	2 wt%
Purified water to	100 wt%

Buffering systems, tensides and consistency agents can be incorporated in the cream for cosmetic purposes.

The cream was prepared in the following manner. The ingredients were mixed and the mixture heated to 70°C. After 15 minutes at this temperature, the mixture was cooled to room temperature at a rate of 1 - 3°C per minute.

The cream was tested on eight patients with moderately severe acne. Former treatments had been terminated at least one week before the treatment of the invention was initiated. Efficacy was evaluated on the basis of the number of papulae and pustules on the face and compared with historical data. Treatment was carried out for 2 - 5 weeks in contrast to the usual 8 weeks which formed the basis of the historical data (see Tables 1 & 2). No side effects were evident. One patient left the study due to periodic dermatitis.

TABLE 1

Calculation of the reduction in number of papulae and pustules

Patient no.	Before		After	
	Papulae	Pustules	Papulae	Pustules
1	72	3	12	0
2	18	13	36	0
3	20	0	0	0
4	29	20	30	2
5	32	4	11	1
6	37	1	0	0
7	46	1	6	0
8	37	1	16	0
Total	451	43	115	3
Percent reduction			74.4	93.0

TABLE 2.

Overall Assessment

	Patients	Doctor's assessment
Much better	3 (37%)	0-25% -
Noticeably better	4 (50%)	26-50% 1
Better	-	51-75% 4
Unchanged	1 (13%)	76-100%3
Worse	-	
Much worse	-	

Example 2

A gel containing the following ingredients was prepared in the same manner as described in Example 1.

Tinidazole	2	wt%
Propylene glycol	20	wt%
Thickening agent	0.5	wt%
Purified water to	100	wt%

The gel was given to patients with seborrhoeic eczema on the scalp. Earlier therapy with known agents had not had any result. When using the gel of Example 2, the patients became symptom free with 2 to 3 applications per week.

Example 3

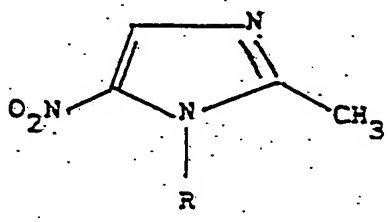
An emulsion with the following composition was prepared:

Liquid paraffin	30	g
Sorbitan mono-oleate	1	g
Polyoxyethylene (20) stearate	1	g
Water	65.6	g
Carbomer	0.4	g
Tinidazole	2	g

The liquid paraffin was mixed with the sorbitan mono-oleate, heated to 70°C and tinidazole then mixed in. The polyoxyethylene (20) stearate, water and carbomer were mixed, homogenized and heated to 70°C. Under vigourous homogenizing, the different partial mixtures were mixed and the temperature allowed to drop to room temperature.

CLAIMS

1. Use of a compound of the formula (I)



(I)

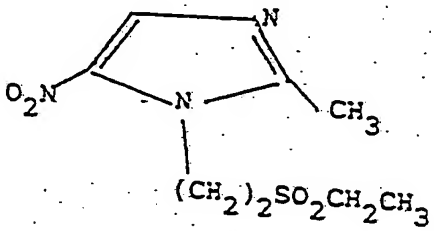
wherein R is:

a) $-(CH_2)_mSO_2(CH_2)_nCH_3$
where m = 2-3 and n = 0-1; or

b) $-(CH_2)_mSO_2CH(CH_3)_2$
where m = 2-3

for the preparation of a pharmaceutical composition for the treatment, especially the topical treatment, of inflammatory and/or infectious skin conditions.

2. The use of a compound of the formula (I) according to claim 1, wherein the compound is ethyl(2-(2-methyl-5-nitro-1-imidazolyl)ethyl)sulfone with the formula:



3. The use of a compound of the formula (I) according to claim 1 or 2 for the preparation of a pharmaceutical composition for the treatment of eczema, especially seborrhoeic eczema.

4. The use of a compound of the formula (I) according to claim 1 or 2 for the preparation of a pharmaceutical composition for the treatment of acne.

5. The use of a compound of the formula (I) according to claim 1 or 2 for the preparation of a pharmaceutical composition for the treatment of rosacea.

6. The use of a compound of the formula (I) according to any one of the preceding claims, wherein the compound is present in the composition in a concentration of 0.25 to 5 weight percent, calculated on the total weight of the composition.

7. The use of a compound of the formula (I) according to claim 6, wherein the concentration of the compound is 0.5 to 2 weight percent, calculated on the total weight of the composition.

8. The use of a compound of the formula (I) according to any one of claims 1 to 7 for the preparation of a pharmaceutical composition in the form of solid surface active crystals.

9. A method for the treatment of inflammatory and/or infectious skin conditions which comprises the administration, preferably topically, of a compound of the formula (I) in a pharmaceutical composition as defined in any one of claims 1 to 8 to a patient afflicted with such a condition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00276

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 31/415
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO, A1, 9203133 (BLOOM LEONARD ET AL), 5 March 1992 (05.03.92) --	1-8
Y	WO, A1, 8806888 (CURATEK PHARMACEUTICALS, INC.), 22 Sept 1988 (22.09.88) --	1-8

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 June 1993	14 -07- 1993
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/SE 93/00276

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/04/93

International application No.
PCT/SE 93/00276

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9203133	05/03/92	AU-A- 6405290	17/03/92
WO-A1- 8806888	22/09/88	AU-B- 610495	23/05/91
		AU-A- 7233787	10/10/88
		EP-A,B- 0305380	08/03/89
		SE-T3- 0305380	